By this amendment, pending Claims 1-49 have been cancelled and new Claims 50-84 have been added to more particularly define Applicants' invention. The support for new Claims 50-84 may be found throughout the specification and in the originally filed claims. Applicants maintain that no new matter has been added to the application by these amendments.

THE INVENTION

Applicants have discovered that certain isolated peptides, derived from pyrogenic exotoxins that induce toxic shock, including, but not limited to Staphylococcus aureus exotoxin B (SEB) are capable of eliciting a protective immune response against toxic shock, as well as directly antagonize toxin-mediated lymphocyte activation. These peptides are substantially homologous to or similar in amino acid sequence to a domain of such exotoxins that is not involved in binding of the toxin to the T-cell receptor (TCR) or to MHC Class II molecules, but forms the central turn in the toxin molecule starting within β-strand 7 and connecting it, via β-strand 8, to α-helix 4 (see Fig. 2). In SEB, this domain encompasses amino acids 150-161 (SEQ. ID NO.: 12). Such isolated peptides directly inhibit pyrogenic toxin-mediated induction of IL-2, INF-γ and/or TNF-β gene expression in normal peripheral blood mononuclear cells (PMBC). The expression of these genes is exquisitely sensitive to toxin (e.g., SEB) mediated activation. Likewise, antibodies against the peptides of the invention also bind to the toxins and can inhibit the

expression of these genes, induced by any of SEB, a related toxin, SEA and a more distantly related toxin TSST-1, all of which can induce toxic shock in an individual.

THE RESTRICTION REQUIREMENT

Original Claims 1-49 were subject to a restriction requirement as follows:

I. Group I, Claims 1-33 and 40 directed to peptides and compositions and a vaccine comprising the peptides.

II. Group II, Claims 34-39 directed to methods of treatment for toxic shock, using the peptides.

III. Group III, Claims 41-46, directed to antibodies to the peptides.

IV. Group IV, covering a kit for assessing vaccination efficacy.

Applicants had provisionally elected to prosecute the claims of Group I in the present invention. Applicants confirm this election, but with traverse, as to Groups I and III -- the peptide and antibody claims.

While alleged by the Examiner to be different products ("physically and functionally distinct chemical entities"), the peptides of Group I and antibody of Group III are actually both classified in the same class (530) and subclass (350). Indeed, the claimed peptides elicit the originally claimed antibodies that carry out the same function, i.e., antagonize the activity of pyrogenic exotoxins. In addition, there would be no extra burden in searching both -- as indicated by the search actually done by the Examiner -- to turn up art that relates to both the peptides and the antibodies to them. It is believed that

a search regarding antibodies would turn up no art that would not also be related to the peptides.

However, at the present time, applicants have provisionally cancelled Claims 41-46 without prejudice in the interests of furthering prosecution. Should the restriction requirement as to Groups I and III be withdrawn, applicants will again present the antibody claims.

Claims 34-39 and 47-49 have been cancelled without prejudice. Applicants expressly reserve the right to present these claims in further divisional applications.

DRAWING REQUIREMENT

Applicants will submit formal drawings upon receipt of a Notice of Allowance in this application.

ABSTRACT

A substitute Abstract has been submitted.

CLAIMS OBJECTIONS

Claim 40 has been objected to as being in improper dependent form. Claim 40 has been cancelled.

REJECTIONS UNDER 35 USC §101

Claims 1-33 stand rejected under 35 USC §101 as allegedly reading on a "product of nature." Claims 1-33 have been cancelled. New claims 50-84 clearly define the claimed peptides as "isolated" or "isolated and purified," thus indicating "the hand of man." In view of these amendments, the Section 101 rejection is moot and should be withdrawn.

REJECTIONS UNDER 35 USC §112, ¶2

Claims 1-33 have been rejected under 35 USC §112, ¶2 as indefinite. The Examiner has objected to the term "substantially homologous" in the claims as rendering the claims ambiguous. Claims 1-33 have been replaced by new Claims 50-84 which retain the term "substantially homologous."

Claims 50-84 are directed to isolated peptides and compositions comprising the peptides wherein the isolated peptides correspond to a particular defined region/domain of pyrogenic toxins that forms the "central turn" of such molecules (see Example 2), and are substantially homologous in sequence to the amino acid sequence of this domain. For example, in an embodiment of the invention, the domain comprises amino acides 150-161 of SEB, whose amino acid sequence is well known (and set forth in SEQ. ID NO.: 12).

Contrary to the Examiner's assertion, in the present case, the term "substantially homologous" is well-defined in the specification as to the claimed

peptides, and those of skill in the art would be readily able to ascertain the metes and bounds of the claims as required by Section 112, ¶2.

For example, page 25, lines 21-27 -- page 26, lines 1-10 discusses sequence homologies among related pyrogenic toxins in the domain of such toxins that forms the "central turn" of such molecules, corresponding to amino acids 150-161 of SEB. The specification clearly provides that the peptides have KKK and QELD motifs that are common to SEB, as well as to the related toxins SEA, SEC1, SEC2 and S. pyogenes exotoxin A (SPE A). Likewise, the meaning of "substantial homology" can be ascertained by the disclosure that the related exotoxin proteins share between 9/12-10/12 amino acid residues with SEB in the region of amino acids 150-161 of SEB (i.e., in the "central turn" domain). See, e.g., Example 2, page 36, lines 16-21, Example 6, page 41, lines 1-13. Moreover, any peptide within the scope of Claim 50 or 51, and claims dependent thereon, must also meet the functional limits set forth in the claim, which are also clear and understandable to someone of skill in the art. In view of the amendments to the claims, the specification and the remarks herein, applicants maintain that those of skill in the art would be able to readily ascertain the metes and bounds of the claims, thereby obviating the §112, ¶2 rejection.

REJECTIONS UNDER 35 USC § 102(b)

Claims 1-18, 13-16, 18, 21, 23 and 26-30 stand rejected under 35 USC § 102(b) as allegedly anticipated by Tseng et al., Infect. Immun. 63(8): 2880-85(1995)

("Tseng et al."). Claims 1-8, 13-16, 18, 21, 23 and 26-30 have been cancelled and replaced by Claims 50-64, 67, 68, 75, 76, and 80-82. Applicants maintain that these new claims are not anticipated by Tseng et al.

Claim 50 is directed to an isolated and purified peptide whose amino acid sequence is substantially homologous to a domain of the pyrogenic toxins that forms a central turn in the molecule starting with β-strand 7 and connecting it, via β- Strand 8, to α-helix 4 (See Fig. 2 and Example 2). Claim 51 provides an isolated and purified peptide substantaially homologous to the amino acid sequence of SEB in this domain (amino acids 150-161 of SEB). Claims 52-65 define various derivatives of the isolated peptide (e.g., dimerized and multimerized forms, conformationally stabilized forms and peptides having N- and C- terminal additions) and specific sequences thereof, while the remaining claims define compositions comprising the isolated peptides. Thus, the present invention is directed to isolated peptides that are derived from, but do not constitute a full length toxin protein.

On the other hand, Tseng et al. teach administration of a SEB toxoid (a full length protein, not a peptide) in microspheres to monkeys in order to elicit neutralizing antibodies to SEB (toxin). Those monkeys that produced such antibodies to the toxoid appeared to survive a subsequent aerosol challenge with SEB. But, Tseng et al. neither teach nor suggest that the toxoid itself antagonizes SEB activity on cell.

It is well known that a toxoid is a chemically-modified full length toxin protein that retains the antigenicity (immunogenicity), but not the toxicity of a toxin

protein. Thus, immunization with a toxoid can lead to production of an immune response to a toxin that, in some circumstances, is protective. For example, this is the basis for immunization against diphtheria and tetanus.

In Tseng et al., SEB toxin (full length protein) had been treated with formalin and then alum precipitated to produce the toxoid used for immunization. However, Tseng et al. never isolated any peptides corresponding to a particular domain of SEB as in the present invention, nor tested the ability of such isolated peptides themselves to inhibit SEB and other toxin (e.g., SEA, TSST-1) - mediated activities, such as activation of IL-2, IFN-γ and TNF-β gene expression, nor produced antibodies to the specific peptide that also inhibit toxin-mediated T cell activation, as in the present invention.

Moreover, as documented in the present specification (see, e.g., page 5, lines 4-10; page 31, lines 1-5; page 43, lines through page 45, line 19 and page 51, lines 10-16), the ability to elicit antibodies to SEB by administration of toxoid, as shown in Tseng et al. is not predictive of whether such antibodies will antagonize (i.e., inhibit) toxin-mediated T-cell activation, nor inhibit toxin-mediated gene expression, as in the present invention. In fact, in some cases, antibodies to certain portions or domains of SEB actually potentiated toxin activity.

For a reference to anticipate a claim under 35 USC § 102(b), the reference must teach each and every limitation of the claim. Scripps Clinic & Research Fdn. v. Genentech, Inc., 18 U.S.P.Q. 2d 1001, 1010-1011 (Fed. Cir. 1991).

Tseng et al. clearly does not teach each and every element of the invention as claimed, which is required for a rejection under Section 102, thereby obviating this rejection. Applicants request reconsideration and withdrawal of the rejection.

Moreover, Tseng et al. does not even suggest the presently claimed invention. There is clearly no suggestion whatsoever in the reference of the claimed isolated peptides and compositions comprising them.

Claims 1-8, 13-16, 18, 21, 23 and 26-33 also have been rejected under 35 USC § 102(b) as anticipated by Lowell et al., Infect. Immun. 64(5): 1706-1713 (1996) ("Lowell et al."). Claims 1-8, 13-16, 18, 21, 23 and 26-33 have been replaced by Claims 50-64, 67, 68, 75, 76, 79-81. For the same reasons, as set forth above, Lowell et al. neither teaches nor suggests the instant invention.

Like Tseng et al., Lowell et al. is directed to the production of anti-SEB antibodies by administration of an SEB toxoid (full -length protein). Again, the isolated peptides of the present invention are not the same as a toxoid and thus, Lowell et al. does not teach each and every element of the claims. It is clear that the isolated peptides of the present invention or their derivatives (e.g. dimerized, multimerized, etc.) are not the same as the toxoid of Lowell et al.

Thus, Lowell et al. does not anticipate the present claims and should be removed as a reference.

REJECTIONS UNDER 35 USC § 103(a)

Claims 1-8, 13-16, 18, 21, 23 and 26-33 have been rejected under 35 USC § 103(a) as obvious in view of Lowell et al. combined with U.S. Patent No. 5,310,874 ("the '874 Patent"). Applicants disagree.

As noted above, the Examiner has misinterpreted Lowell et al. as it applies to the present invention. Lowell et al. teach the use of a SEB toxoid (full length protein) to elicit antibodies to SEB. The present invention claims isolated peptides corresponding to a particular domain of pyrogenic toxins that forms the "central turn" of such molecules (e.g., amino acids 150-161 of SEB) which is highly conserved in related pyrogenic exotoxin proteins. Lowell et al. provide no suggestion whatsoever about making the isolated peptides of the present invention, nor that such peptides can directly antagonize toxin-mediated T cell activation, as measured by inhibition of toxin mediated expression of IL-2, INF-γ and TNF-β genes. Moreover, the differences between Lowell et al. and the present invention are discussed at various places in the specification (See e.g., page 4, lines 1-10; Example 7, especially at page 44, lines 6-17; Example 8, page 45, line 20-, page 46, line 6).

The '874 patent merely discloses the already known use of KLH and alum as adjuvants in enhancing antibody production, which is only relevant to Claims 30-33 (but not to the remaining Claims).

Since the primary reference Lowell et al. fails to teach or suggest the claimed isolated peptides, its combination with the '874 patent in regard to Claims 30-33 also fails.

In view of the amendments to the claims and the remarks herein, applicants maintain that the presently claimed invention is not obvious over Lowell et al., either alone or in combination with the '874 patent.

CLAIMS 9-12, 17, 19-20, 22 AND 24-25

Applicants acknowledge that the above-referenced claims have been deemed free of the prior art. However, these claims have been rewritten as Claims 66, 67, 70-75, 78, 83 and 84 to more particularly define the present invention. It is believed that these new claims are also free of the art and patentable.

Conclusion

In view of the amendments to the claims and abstract and the remarks herein, Applicants maintain that Claims 50-84 are now in condition for allowance. A Notice of Allowance is solicited

Respectfully submitted,

Rochelle K. Seide

Rochelle K. Seide
Patent Office Reg. No. 32,300

Attorney for Applicants
(212) 408-2626